DETAILED ACTION

Claims Under Examination

Claims 1, 2, 4, 6, 9-14, 16, 31, 36-42, and 45-56 are under examination.

Claims 3, 5, 7, 8, 15, 17-30, 32-35, 43, and 44 have been cancelled.

Priority

Priority to provisional application 60/213,658, filed 06/23/2000, is acknowledged.

Information Disclosure Statement

The information disclosure statement filed 02/29/2008 has been considered in full.

Withdrawn Rejections

The rejection of claims 1, 2, 4, 6, 9-14, 16, 31, 36-42, and 45-56 are rejected under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicant's amendment of claims 1, 31, and 48, filed 02/29/2008.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
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> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4, 6, 9-14, 16, 31, 36-42, and 45-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zou et al (J. Am. Chem. Soc., 1999, Vol. 121, p.8033-8043), in view of Bassolino et al. (Protein Science, 1996, Vol. 5, p.593-603).

Zou et al. teaches a computer- assisted method for modeling ligand-receptor binding interactions [Abstract]. In particular, Zou et al. teach the following aspects of independent claims 1, 31, and 48:

- Obtaining structural information from crystal structures to identify binding regions [p.8037, col.1-2, III, Results, § 1].
- Applying DOCK (i.e. coarse-grain search algorithm) is used to identify 10,000 top force field scoring molecules and rank the selected candidates [p. 8037, col.2, Section 2], and selecting the best scoring conformations based on lowest energy [Table 4]. Furthermore, as DOCK is a well-known as a method of force-field scoring, which is a teaching for optimization using "molecular mechanics" (See www.answers.com definition).
- Calculating binding energies using a GB/SA (i.e. simulated annealing) model of solvation [p.8034, Col. 1, Section 1] and calculation of binding energies for each ligand where the binding energies [EQUATION 8].
- Ranking of candidates for selection of optimal conformations based on binding energy [p.8037, Col. 2, Section 2] and [p.8037, Section 6].
- Outputting top scoring candidates from a database [p.8040, Col. 1, ¶ 3] and [Tables 2 and 3] and top scoring orientations with DOCK [Table 4], which shows outputting a data files of selected conformations as programs inherently output data.
- All above computations are done using software and a Silicon Graphics workstation [Abstract], therefore the Examiner has reasonably interpreted the method and algorithms of Zou et al. as a an implicit teaching for a computer program product and system, as in claims 31 and 48.

Zou et al. also teaches the following aspects of the following dependent claims. Ranking of known binding regions is performed [p.8037, Col. 2, Section 2], as in instant claim 2. Scoring of ligand molecules is based on the grid spacing of 0.3 A (first energy function) and distance cutoff of 10A (second energy function), where orientation (i.e. conformation) minimization is performed and the results are given in Table 1 (page 8037, column 2, lines 1-19 and Table 1), as in instant

claims 4-6, and 8. Effective Born radii calculations [p.8036, Col. 2, Section 2] enable spatial selection of optimal conformations within an energy grid, wherein the Examiner has broadly interpreted as 'spatial clustering' as in claims 4, 36. Zou et al. discloses a continuum solvent model [p.8035, Section 3] and EQUATIONS 4, 5, and 6 which clearly incorporate surface area into their model, as in instant claims 10, 11, 38, and 39. EQUATION 8 enables calculation of binding energy for each ligand where the binding energies are represented as the difference G_{LR} - G_L- G_R in solvent (where L= ligand, R=receptor/protein), as in instant claims 12 and 14, and account for binding energy dependence on water [p.8037, Col. 1, ¶2], as in claims 13, 41, and 49. Binding energy for each ligand is calculated by taking the difference in the ligand energy of ligand in solvent and in receptor (page 8035, columns 2, §3 and §4 to page 8036, column 1), as in instant claims 12, 40, and 42. Zou et al. disclose methods directed to globular protein and the calculation of dielectric constant of said protein in water (page 8035, column 1, lines 3-12), as in instant claim 16. Zou et al. teach the treatment of solvent molecules in molecular dynamics simulations (page 8033, column 2, lines 14-15), where unoccupied embedded space between ligand and the receptor (empty volume) is penalized and energy minimization is performed with DOCK force field scoring (i.e. full atom force field), as in instant claims 9 and 37. The GB/SA model computes ligand binding energies wherein the parameters are approximated by a linear dependence on the solvent-accessible surface area and dielectric properties around the binding site as directed to the unoccupied embedded space (page 8034, 11. Method §, column 2, to page 8035, column 1, line 26). The first set of parameters yields the best fit binding energies six inhibitors (subset). TMP and MTX rank no. 1 and no. 2 among top scoring 10,000 ACD molecules for dhfr (page 8040, column 1, lines 10-19), as in instant claim 45. Scoring functions based on subtraction of free energies [EQUATIONS 15 and 16, p.8037], as in claims 46 and 47.

Zou et al. do not specifically teach the "calculated percentage of ligand surface area" limitation of claims 6, 45, and 56. However, EQUATION 11 clearly calculates the change in

hydrophobic and total solvent-accessible surface areas for selecting optimal conformations [p.8036] and uses predefined grids for evaluating protein-ligand biding based on Born-radii areas [Fig. 2]. Thus, it would have been well within the ordinary capabilities of one skilled in the art select the best conformations based on percentage calculations of ligand surface area buried within a protein.

Zou et al. do not specifically teach Monte Carlo methods, as in claims 53-55. However Zou teaches that Monte Carlos simulations are obvious methods for simulation of binding interactions. Thus, it would have been well within the ordinary capabilities of one skilled in the art select the best conformations using Monte Carlo algorithms.

Zou et al. do not specifically teach a step for "further optimizing a subset of the best conformations" using annealing molecular dynamics including solvation effects, as in claims 1, 9, 31, 37, 48, 50, 51, and 52.

Bassolino et al. teach a program (CONGEN) for molecular structure generation that uses several search algorithms including MD with the CHARMM (full atom force field) potential energy function [p.594, Col. 1, ¶4], as well as simulated annealing molecular dynamics (SA-MD) procedures for generating 3-D protein structures [Fig. 3, below], as in claims 1, 9, 31, 37, 48, 50, 51, and 52. In particular, Bassolino teaches a step wherein the final structures were further refined by energy minimization in CONGEN and resulting coordinates are stored for analysis [p.602, Col. 2, ¶2]. Therefore it would have been well within the capabilities of one of ordinary skill in the art to further optimize any subset of conformations using the methods disclosed by Bassolino and Zou, as required by claims 1, 9, 31, 37, 48, 50, 51, and 52.It would have been obvious to one of ordinary skill in the art at the time of the invention to use the SA-MD optimization algorithm of Bassolino et al. for identifying optimal ligand conformations according to the method Zou et al., since Zou et al. suggest the combination of molecular dynamic computations including

solvation effects [page 8033, column 2, lines 14-15], and since Bassolino suggests that computational techniques for determining protein structures using docking algorithms using simulated annealing are well known in the art [p.593], resulting in the practice of the instant claimed invention with predictable results. One of ordinary skill in the art would have been motivated to use the SA-MD optimization procedure for the improvements it provides over other programs by allowing users to control weights on individual constraints throughout the annealing procedure, as suggested by Bassolino et al. [p.594, Col. 2, ¶ 1].

Claims 1, 2, 9, 31, 37, 48, and 50-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vieth et al. (Journal of Computational Chemistry, 1998, Vol. 19, No. 14, p.1623-1631), in view of Moyna et al. (Biopolymers, 1999, Vol. 49, p.403-413).

Vieth et al. teach methods for identifying one or more ligand conformations that bind to a protein including molecular dynamics (MD), Monte Carlo (MC), and genetic algorithm (GA) methods [Abstract]. More specifically, Vieth et al. teach the following aspects of the instant invention:

- Obtaining structural information and binding regions from known ligand-receptor complexes in a database [p.1624, Col. 2, ¶2], as in claims 1, 2, 31, and 48.
- Three-stage docking protocol wherein the first stage identifies a plurality of binding conformations to known structures using docking algorithms including Monte Carlo (i.e. coarse-grained docking algorithm) [Table III], the second stage includes annealing for MC and MD for finding local minima, and the third stage further minimizes structures based on temperature quenching [p.1626, Col. 2, ¶ 1], as in claims 1, 31, 48, and 53-55.

- Calculating individual and mean binding energies of lowest energy structures (i.e. preferred conformations) [p.1629, Col. 1, ¶ 2] and statistical ranking of structures preferred structures (i.e. within 1 angstrom) [Table II], as in claims 1, 31, and 48.
- Outputting the fraction of docked structures within 1 angstrom RMSD of the crystal structure [Table III] wherein all computations are done via computer workstations [p.1631, Col. 1, ¶ 2], which is an implicit teaching for outputting data files of selected ligand-protein conformations having lowest calculated binding energy as in claims 1, 31, and 48.
- All above computations are done using software and a Silicon Graphics workstation [p.1631, Col. 1], therefore the Examiner has reasonably interpreted the method and algorithms of Zou et al. as a an implicit teaching for a computer program product and system, as in claims 31 and 48.

Vieth et al. do not teach specifically teach optimization using "annealing molecular dynamics including solvation effects", as in claims 1, 9, 31, 37, 48, 50, 51, and 52.

Moyna et al. teach computer assisted methods for molecular modeling wherein conformer sets are generated by restrained simulated annealing experiments running on computer systems [p.411, Col. 2]. The AMBER force field program is used to simulate solvent effects. Specific ranges were assigned for ranking interactions. Simulated annealing experiments are followed by minimization of the resulting structures to an energy gradient below a specific threshold [p.412, Col. 1]. Initial conformations used in annealing experiments were generated by distance geometry and optimized for lowest energy. Molecular dynamics are performed using TINKER program on a supercomputer. AMBER 95 force field and charges are used and include implicit GB/SA solvation started from the lowest energy conformer obtained by simulated annealing. A total of 5000 structures are generated. Structure analysis was performed using MSS [p.412, Col. 1].

Therefore, Moyna et al. provide evidence for optimization based on annealing molecular dynamics including solvation effects and energy minimization of conformations 1, 9, 31, 37, 48, 50, 51, and 52.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to use the SA-MD optimization algorithm of Moyna et al. for identifying optimal ligand conformations according to the method Vieth et al., since Vieth et al. suggests the use of methods for simulation of solvent effects (which are based on dielectric constants) [p.1625, Col. 1, ¶2, and also see www.answers.com definition for solvation], and since Vieth et al. suggests docking algorithms that utilize simulated annealing [p.1624], resulting in the practice of the instant claimed invention with predictable results. The motivation to use the SA-MD optimization procedure is provided by Moyna et al., who suggest their model is an efficient method for MD simulations that could be applied with similar results to other small peptides for designing novel environmentally safe insect management agents [p.411, Conclusions].

Response to Arguments

Applicant's arguments, filed 02/29/2008, that the cited references do not teach the hierarchy of steps as claims [p.4] have been fully considered but are not persuasive for the following reasons.

Zou teaches obtaining structural information from crystal structures to identify binding regions [p.8037, col.1-2, III, Results, § 1]. Zou uses a coarse-grain search algorithm to identify top force field scoring molecules [p. 8037, col.2, Section 2]. Zou selects the optimum scoring conformations based on lowest energy [Table 4]. Zou calculates binding energies using a GB/SA model of solvation [p.8034, Col. 1, Section 1]. Zou ranks candidates for selection of optimal

conformations based on binding energy [p.8037, Col. 2, Section 2] and [p.8037, Section 6]. Zou teaches outputting top scoring candidates [p.8040, Col. 1, ¶ 3, Tables 2 and 3] and top scoring orientations with DOCK [Table 4], which shows outputting a data files since programs inherently output data. Zou does not specifically teach a step for "further optimizing a subset of the best conformations" using molecular dynamics. Bassolino teaches further refinement of optimal structures using simulated annealing molecular dynamics (SA-MD) [p.594, Col. 1, ¶4, Fig. 3,, and p.602, Col. 2, ¶2]. Therefore it would have been obvious to of one of ordinary skill in the art to further optimize any subset of conformations using the methods disclosed by Bassolino and Zou. The motivation to use SA-MD optimization procedures would have been the improvements it provides over other programs by allowing users to control weights on individual constraints throughout the annealing procedure, as suggested by Bassolino et al. [p.594, Col. 2, ¶ 1].

Vieth teaches methods for identifying one or more ligand conformations that bind to a protein using molecular dynamics (MD), Monte Carlo (MC), and genetic algorithms (GA). More specifically, Vieth teaches obtaining structural information and binding regions from known ligand-receptor complexes in a database [p.1624, Col. 2, ¶2]. Vieth teaches identifying a plurality of binding conformations to known structures using docking algorithms including Monte Carlo (i.e. coarse-grained docking algorithm) [Table III], and teaches annealing in MC and MD for finding local minima, and further minimizes structures based on temperature quenching [p.1626, Col. 2, ¶ 1]. Vieth teaches calculating individual and mean binding energies of lowest energy structures (i.e. preferred conformations) [p.1629, Col. 1, ¶ 2] and statistical ranking of structures preferred structures (i.e. within 1 angstrom) [Table II]. Vieth teaches outputting results [Table III, and [p.1631, Col. 1, ¶ 2]. Vieth does not teach optimization using "annealing molecular dynamics including solvation effects", as in claims 1, 9, 31, 37, 48, 50, 51, and 52. Moyna teaches molecular modeling using simulated annealing [p.411, Col. 2], wherein the AMBER force field program includes solvent effects [Also see p.412, Col. 1, and p.412, Col. 1]. Therefore, Moyna

provides evidence for optimization based on annealing molecular dynamics including solvation effects. It would have been obvious to one of ordinary skill in the art at the time of the invention to use the SA-MD optimization algorithm of Moyna et al. for identifying optimal ligand conformations according to the method Vieth et al., since Vieth et al. suggests the use of methods for simulation of solvent effects (which are based on dielectric constants) [p.1625, Col. 1, ¶2, and also see www.answers.com definition for solvation], and since Vieth et al. suggests docking algorithms that utilize simulated annealing [p.1624]. The motivation to use the SA-MD optimization procedure would have been to use an efficient method for MD simulations that could be applied with similar results to other small peptides for designing novel environmentally safe insect management agents, as suggested by Moyna [p.411, Conclusions].

.Therefore the cited combination of references make obvious the hierarchy of steps required by the instant claims.

Applicant's arguments, filed 02/29/2008, that it would not have been obvious to one of ordinary skill in the art to combine the above references [p.8] in view of the Declaration filed 2/29/2008 by William A. Goddard, III, under 37 CFR 1.132, which asserts surprising and unexpected results, commercial success, and long-felt need [p.9] have been fully considered but are not persuasive for the following reasons. Applicant's additional arguments directed the also not persuasive for the reasons set forth below.

The Declaration under 37 CFR 1.132 filed 02/29/2008 is insufficient to overcome the rejection of claims 1, 2, 4, 6, 9-14, 16, 31, 36-42, and 45-56 under 35 U.S.C. 103(a) as being unpatentable over Zou et al, in view of Bassolino et al., and the rejection of claims 1, 2, 9, 31, 37, 48, and 50-55 under 35 U.S.C. 103(a) as being unpatentable over Vieth et al., in view of Moyna et al., as set forth in the last Office action because:

It refer(s) only to the system described in the above referenced application and not to the individual claims of the application. Thus, there is no showing that the objective evidence of nonobviousness is commensurate in scope with the claims. See MPEP § 716. The Declaration does not point out which specific claim limitations or combination constitute a surprising and unexpected result, therefore the Declaration does not provide support for a nexus between the claimed invention and surprising or unexpected results. In addition, the Declaration also does not provide support for a surprising and unexpected result based on the order of the claimed method steps. It is noted that the Declaration was provided by William A. Goddard, III, who is not a disinterested party.

It include(s) statements which amount to an affirmation that the claimed subject matter functions as it was intended to function. This is not relevant to the issue of nonobviousness of the claimed subject matter and provides no objective evidence thereof. See MPEP § 716. The Declaration submitted by applicant essential cites references [Section IV] and repeatedly asserts that the claimed invention possesses unexpected advantages. However, it is well settled that unexpected results must be established by factual evidence. Applicants have not presented any experimental data showing that the claimed hierarchy of steps results in an unexpected advantage. Due to the absence of tests comparing applicant's claimed method steps with those of the closest prior art, applicant's assertion of unexpected results constitute mere opinion evidence. See also In re Linder, 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1972; Ex parte George, 21 USPQ2d 1058 (Bd. Pat. Appl. & Inter. 1991).

It asserts that the claimed subject matter is commercially successful [Section V]. The assertion of commercial success requires establishing a nexus between the claimed invention and evidence of commercial success. However, there is no disclosure of the specific features of the instant claims that are responsible for the asserted commercial success. Therefore the Declaration

does not provide evidence of commercial success that is commensurate in scope with the claims at issue. See MPEP § 716.03.

It states that the claimed subject matter solved a problem that was long standing in the art. However, there is no showing that others of ordinary skill in the art were working on the problem and if so, for how long. In addition, there is no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references, they would still be unable to solve the problem. See MPEP § 716.04.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pablo Whaley whose telephone number is (571)272-4425. The examiner can normally be reached on 9:30am - 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached at 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Pablo S. Whaley/

Patent Examiner

Art Unit 1631

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Primary Examiner, Art Unit 1631